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Offset analgesia as a marker of dysfunctional pain modulation in episodic and chronic migraine

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Abstract

Background The offset analgesia phenomenon refers to the disproportionately large decrease in the perceived pain following a slight decrease in intensity of a noxious heat stimulus. It is considered an expression of the activation of the endogenous pain-modulation system. The main aim of this study was to examine pain processing using the offset analgesia paradigm in subjects with interictal episodic migraine compared to those with non-ictal chronic migraine. Additionally, as secondary outcome measures, we aimed to: (1) explore fluctuations in the endogenous pain modulation system throughout the migraine cycle by including small subgroups of episodic migraine patients in different migraine phases, and (2) compare different subgroups of non-ictal chronic migraine patients with or without medication overuse headache (MOH).

Methods A total of 68 subjects with episodic migraine (different subjects were evaluated during the interictal, preictal, ictal, or postictal phase), 34 with non-ictal chronic migraine with or without MOH, and 30 healthy controls were enrolled. Participants underwent six trials involving constant temperature and stimulus offset applied to the forehead, with pain responses measured using a continuous analogue-to-digital converter of VAS.

Results The offset analgesia phenomenon was recorded predominantly during the postictal phase among the population of episodic migraine patients, as well as in healthy subjects. Offset analgesia was generally absent in interictal episodic migraine subjects and in subjects with chronic migraine with MOH, though some individual variability was observed. A paradoxical increase in pain facilitation was observed in most preictal and ictal episodic migraine subjects, as well as in chronic migraine subjects without MOH. The severity of offset analgesia impairment correlated with scores on the Allodynia Symptom Checklist and the Numeric Pain Rating Scale, which assessed average headache intensity during untreated migraine attacks.

Conclusions Episodic and chronic migraine patients exhibit disrupted top-down pain modulation pathways, with more significant alterations in chronic migraine without MOH. Additionally, we provide preliminary evidence that cyclical changes in the endogenous pain modulation system could contribute to migraine recurrence in episodic migraine sufferers. However, given the small subgroups of interictal patients evaluated in different migraine phases

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and the cross-sectional study design, these findings should be interpreted with caution and confirmed by future longitudinal studies with larger sample sizes.

Keywords Pathophysiology of migraine, Descending pain control system, Dynamic nociceptive stimulation, Offset analgesia, Rostral ventromedial medulla, Migraine chronification

Introduction

Migraine is a chronic disease with recurrent acute attacks characterized by fluctuating changes in the activity of various areas of the brain and brainstem [1–3]. There is a general assumption of a pro-nociceptive pain modulation pattern in migraine, which could be at least partly due to impaired endogenous pain inhibitory systems [4, 5]. However, there is a surprising paucity of studies in this regard, and the use of different experimental paradigms has led to conflicting results, showing either normal [6–10] or abnormal [8, 11–14] responses to pain stimuli in migraine. Moreover, almost all studies have assessed only subjects with episodic migraine in the headache-free interval. Thus, the role of dysfunctional pain modulation in the recurrence of migraine attacks and the tendency of migraine to evolve, in some individuals, from an episodic to a chronic pattern remains unexplained.

Offset analgesia is a psychophysical paradigm increasingly used to assess the functioning of descending pain modulation systems in different chronic pain disorders [15]. Offset analgesia assesses temporal filtering mechanisms engaged when dynamic noxious stimuli are applied [16]. It is defined as a disproportionately large decrease in pain sensation following a tiny decrease in a heat pain stimulus applied to the skin [15, 17]. Offset analgesia has at least partially distinct underlying mechanisms compared to Conditioned Pain Modulation (CPM), probably the most used tests to examine inhibitory pain modulation capabilities based on the spatial filtering of pain by the 'pain inhibits pain' phenomenon [18]. While peripheral mechanisms may contribute to offset analgesia [19], behavioural studies [20–22], neuroimaging research [18, 23–25], and computational modelling [22, 26] suggest that central mechanisms are primarily involved. These include activation of both the descending pain modulatory and the reward systems [17, 27, 28]. Research in chronic pain populations, including those with neuropathic pain and migraine, has revealed reduced or absent offset analgesia responses, suggesting dysfunction in these central mechanisms [4, 17]. In migraine, this dysfunction may be linked to changes in brain areas such as the periaqueductal gray and rostral ventromedial medulla, which are implicated in the modulation of pain during different phases of the migraine cycle [3, 29].

To date, a single study has tested the response to the offset analgesia paradigm in a group of subjects with episodic migraine [4], revealing absent inhibitory pain modulation in the trigeminal area during the headache-free interval. Considering its potential as a marker of dysfunctional pain control in migraine, assessing offset analgesia in various phases of the migraine cycle and in chronic migraine patients could provide valuable insights into the mechanisms of attack recurrence and chronification.

The primary objective of the present study was to use the offset analgesia paradigm to evaluate whether distinct dysfunctional patterns of dynamic pain modulation underlie episodic and chronic migraine. Our a priori hypothesis was that individuals with chronic migraine would exhibit greater dysfunction in the response to the offset analgesia paradigm compared to those with episodic migraine. As secondary outcomes, we explored whether the response to the offset analgesia paradigm would change across the migraine cycle, and whether distinct response patterns are evident in individuals with non-ictal chronic migraine with or without medication-overuse headache (MOH).

Materials and methods

Subjects

Participants with episodic migraine, with or without aura, and with chronic migraine, with or without MOH according to the International Headache Society (IHS) Classification [30, 31] were included. All patients were recruited from the Headache Unit of IRCCS Mondino Foundation (Pavia, Italy) between January 2022 and January 2024. Age- and gender-matched healthy volunteers (HVs) without a personal history of migraine or first-degree relatives with migraine were also included, recruited from the institute's staff and among partners or friends accompanying migraine patients. All subjects, including both migraine patients and healthy controls, were examined in the morning, within a time window between 9:00 AM and 1:00 PM, to minimize potential circadian influences on pain perception and offset analgesia responses. Different subgroups of participants with episodic migraine were assessed during various phases of the migraine cycle, all confirmed via a prospective headache diary and a telephone call after the experimental session: (1) interictal phase, defined as being migraine-free for at least 24 h before and 48 h after the experimental assessment (according to Peng and May [32]); (2) preictal phase, defined as the 48 h prior to the onset of a migraine attack; (3) ictal phase, during which subjects experienced a migraine attack; and (4) postictal phase, defined as up to 24 h after the ictal phase [32]. Participants with chronic migraine, with or without MOH, were evaluated

during periods without headache exacerbations, the latter being defined by a headache intensity > 6 on a 0–10 Numeric Pain Rating Scale (NPRS) and migraine associated symptoms, reflecting the moderate to severe pain levels typically linked to migraine attacks [33]. Additionally, the pain intensity was required to remain ≤ 6 during the 24 h prior to and after the evaluation.

Exclusion criteria included any other headache diagnosis according to the IHS classification and, for both HVs and migraine subjects, acute or chronic pain conditions, clinically significant insomnia, and serious internal, psychiatric, or neurological diseases. Clinically significant insomnia was defined as sleep difficulties occurring at least three times per week, persisting for at least three months, and significantly impairing daytime functioning. Subjects with mild or transient sleep disturbances (e.g., occasional difficulty falling or staying asleep, early awakenings, or non-restorative sleep occurring intermittently but without major daytime impairment) were not excluded, as these are common in both the general population and individuals with migraine, without necessarily fulfilling the criteria for an insomnia disorder (see Table 1). Additionally, pregnancy, breastfeeding, skin pathologies in the tested trigeminal nerve area (V1), poor sleep quality the night before testing (defined as a self-reported poorer sleep than usual or a deviation in total sleep duration of more than 20% from the participant's typical pattern), and alcohol consumption or intense exercise within 24 h prior to the examination were also considered as exclusion criteria. Women were not tested during their menstrual period. However, testing did not occur in the same phase of the menstrual cycle, and women undergoing hormonal therapy were not excluded (Table 1), in line with evidence suggesting that offset analgesia is independent of sex and menstrual cycle phase [34]. Use of migraine preventive medication was an exclusion criterion for subjects with episodic migraine. For participants with chronic migraine, with or without MOH, concurrent use of a single preventive migraine treatment was permitted only if stable for at least three months. Botulinum toxin and migraine-specific preventive drugs targeting Calcitonin Gene-Related Peptide (CGRP) were excluded due to their direct effects on nociceptive mechanisms.

Subjects with episodic migraine, chronic migraine without MOH, and HVs were excluded if they had taken acute pain medication within the last 48 h. For patients with chronic migraine with MOH we chose a narrower window of 24 h to avoid rebound headache.

The recruitment process, including the number of subjects initially contacted, excluded based on screening criteria, and included in the final analysis, is summarized in Fig. 1.

Written informed consent was obtained from all participants. The study adhered to the principles of the Declaration of Helsinki, and the experimental procedures were approved by the local ethics committee (IRCCS San Matteo Polyclinic in Pavia, p-20210047886). The study was retrospectively registered on ClinicalTrials.gov with the identifier NCT06599905.

Study procedures

All subjects underwent a single experimental session. Participants were asked to complete the questionnaires listed in the next paragraph. Subsequently, the Warm Detection Threshold (WDT) and then the heat pain threshold corresponding to a Visual Analog Scale (VAS) score of approximately 50–60 out of 100 ($Pain_{50-60}$) were assessed at the forehead (1st branch of the trigeminal nerve, V1), followed by the assessment of three constant trials and three offset trials in the same area. We applied the stimulation to the trigeminal area based on previous evidence suggesting that alterations in pain processing and modulation in migraine may primarily or exclusively manifest in the affected area or adjacent area [4, 12, 35]. Of note, the WDT was assessed to explore potential variations in warm temperature perception during the migraine cycle, independently of whether the stimulus causes pain.

The examination was scheduled according to the subject's availability. In the case of pain medication intake within 48 h prior to the exam for the participants with episodic migraine or chronic migraine without MOH, and for HVs, the experimental evaluation was rescheduled. Rescheduling was also put in place for participants with chronic migraine with MOH who took an acute drug within 24 h prior to the test session and for the subjects with chronic migraine enduring an exacerbation immediately before or during the test.

Headache features and questionnaires

In addition to demographic data collected in all participants, headache features were assessed by participants interview and review of the clinical history and headache diary. The following information was collected: disease duration, predominant headache side, presence of aura symptoms, mean headache intensity during a migraine attack assessed by NPRS, mean attack duration, mean number of days with mild or moderate-to-severe intensity headache over the last three months, mean number of symptomatic medications taken in the last three months, mean number of days in which symptomatic medications have been taken in the last three months (Table 1). The following questionnaires were also administered: 12-item Allodynia Symptom Checklist (ASC-12), Migraine Disability Assessment (MIDAS), and Hospital Anxiety and Depression Scale (HADS) for assessing

Table 1 Characteristics of participants with episodic or chronic migraine and healthy controls

	Episodic migraine					Chronic migraine			Healthy controls	*P*-value
	Total (*n* = 68)	**Interictal (*n* = 31)**	**Preictal (*n* = 11)**	**Ictal (*n* = 12)**	**Postictal (*n* = 14)**	**Total (*n* = 34)**	**Without MOH (*n* = 11)**	**With MOH (*n* = 23)**	**(*n* = 30)**	
Age, years (SD)	44 (12)	43 (12)	49 (5)	36 (12)	47 (13)	45 (13)	50 (14)	43 (13)	38 (18)	*P* = 0.07
Female, n (%)	51 (75)	20 (64)	9 (82)	12 (100)	10 (71)	31 (94)	10 (91)	21 (91)	19 (63)	*P* = 0.06
Day from the last menstrual cycle, mean (SD)	13.9 (7.4)	13.9 (7.3)	19.3 (6.2)	11.8 (7.4)	11.8 (7.3)	15.0 (8.2)	17.5 (10.6)	14.0 (7.4)	15.3 (11.0)	*P* = 0.81
Under contraception, n (%)	9 (18)	4 (20)	1 (11)	2 (17)	2 (20)	4 (11)	2 (20)	2 (10)	3 (16)	*P* = 0.85
Disease duration, years (SD)	22 (13)	21 (13)	29 (12)	18 (11)	22 (16)	24 (16)	24 (23)	23 (13)	-	*P* = 0.59
Aura, n (%)	11 (16)	5 (16)	1 (9)	2 (17)	3 (21)	6 (18)	1 (9)	5 (22)	-	*P* = 0.92
Dominant headache side: left, n (%); right, n (%); both, n (%)	left 15 (22); right 22 (32); both 31 (46)	left 8 (26); right 9 (29); both 14 (45)	left 3 (27); right 5 (46); both 3 (27)	left 1 (8); right 3 (24); both 8 (66)	left 4 (28); right 4 (28); both 6 (44)	left 7 (21); right 7 (21); both 20 (58)	left 4 (36); right 2 (18); both 5 (46)	left 3 (13); right 5 (22); both 25 (65)	-	*P* = 0.52
Days with moderate-to-severe headache per month, n (SD)	3 (3)	3 (4)	2 (1)	5 (4)	3 (3)	12 (8)	9 (8)	13 (8)	-	***P* < 0.0001**
Days with mild headache per month, n (SD)	4 (4)	3 (5)	5 (5)	4 (3)	3 (3)	10 (7)	12 (6)	9 (8)	-	***P* < 0.0001**
Headache intensity during untreated attacks, NPRS, range 0–10 (SD)	7 (2)	7 (2)	8 (1)	7 (2)	7 (2)	8 (1)	8 (1)	8 (2)	-	***P* = 0.02**
Monthly acute medications, n (SD)	4 (4)	4 (4)	4 (5)	6 (4)	3 (2)	25 (33)	3 (2)	35 (36)	-	***P* < 0.0001**
Monthly days of intake of acute medication, n (SD)	4 (3)	3 (4)	4 (3)	5 (4)	3 (1)	13 (10)	3 (2)	18 (8)	-	***P* < 0.0001**
MIDAS, score (SD)	16 (17)	13 (15)	26 (22)	19 (17)	9 (14)	66 (44)	53 (26)	73 (50)	-	***P* < 0.0001**
ASC-12, score (SD)	4 (4)	3 (4)	6 (4)	6 (4)	5 (3)	6 (5)	6 (4)	6 (5)	-	***P* = 0.02**
Mild or transient sleep disturbances, n (%)	15 (22)	8 (26)	3 (27)	2 (16)	2 (14)	12 (35)	4 (36)	8 (35)	5 (17)	*P* = 0.31
HADS, subscore A score (SD)	6 (4)	6 (3)	6 (5)	7 (4)	7 (5)	6 (4)	6 (3)	6 (4)	-	*P* = 0.57
HADS, subscore B score (SD)	5 (4)	5 (3)	5 (3)	6 (4)	6 (5)	6 (4)	7 (4)	6 (4)	-	*P* = 0.13
Prophylactic therapy	-	-	-	-	-	-	2 amitriptyline (1 24 mg/day; 1 20 mg/day), 2 calcium channel blockers (1 flunarizine 10 mg/day, 1 cinnarizine 48 mg/day), 1 topiramate (75 mg/day), 1 propranolol (80 mg/day)	3 duloxetine (60 mg/day), 4 gabapentinoid (2 gabapentin 600 mg/day; 1 pregabalin 100 mg/day; 1 pregabalin 150 mg/day), 2 topiramate (100 mg/day), 1 propranolol (80 mg/day)	-	
Overused acute medication(s)	-	-	-	-	-	-	-	10 NSAIDs, 5 triptans, 2 paracetamol, 6 analgesic in combination	-	

P values indicate the statistical significance of comparisons among the three groups (healthy volunteers, episodic migraine and chronic migraine) or between subjects with episodic or chronic migraine only. One-way ANOVA, chi-squared test with continuity correction (Yates' correction), or independent t-tests were used, as appropriate. Significant values are indicated in bold

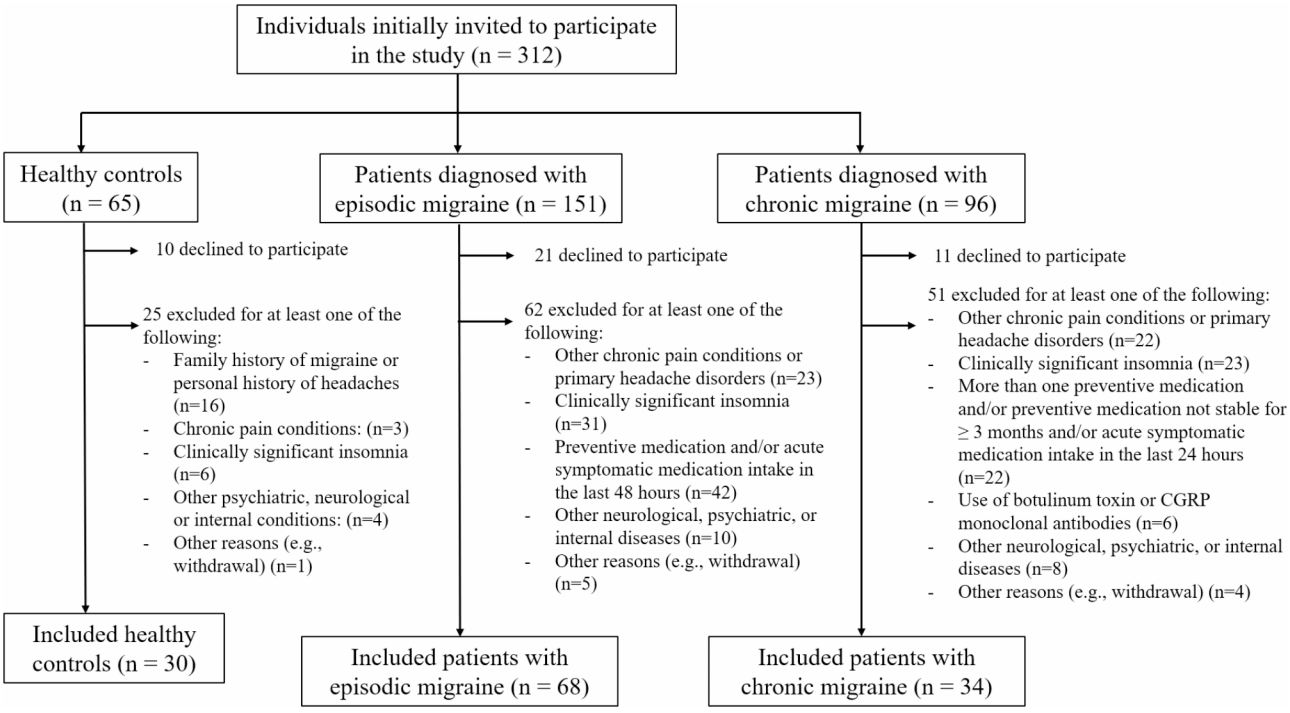

Fig. 1 Flowchart of the recruitment process. The diagram illustrates the number of subjects contacted, those who declined participation, exclusions based on eligibility criteria, and the final number of participants included in the study for both migraine patients and healthy controls

Table 2 Presents the WDT and $Pain_{50-60}$ values across different subgroups, reported as mean ± standard deviation (SD) along with the minimum-maximum range

		WDT	Pain50-60
Group		**Mean ± SD (min-max)**	**Mean ± SD (min-max)**
Healthy controls		32.7 ± 1.5 (32.1–35.0)	42.7 ± 3.5 (36.2–48.7)
Episodic migraine	Interictal	32.8 ± 1.4 (31.1–36.8)	40.5 ± 3.9 (34.2–48.6)
	Preictal	33.1 ± 0.9 (32.1–35.0)	39.6 ± 3.8 (33.9–46.6)
	Ictal	32.5 ± 1.3 (32.1–36.6)	38.1 ± 3.0 (34.8–43.4)
	Postictal	33.1 ± 0.9 (32.1–35.3)	40.7 ± 4.7 (34.5–47.3)
Chronic Migraine	With MOH	33.0 ± 1.2 (32.0-36.4)	41.4 ± 3.9 (34.7–49.4)
	Without MOH	33.8 ± 2.7 (32.1–40.6)	41.9 ± 2.8 (37.7–45.9)

Values of Warm Detection Threshold (WDT) and $Pain_{50-60}$ for the different subgroups analyzed

self-reported patient levels of anxiety and depression in the previous week (Table 2).

ASC-12, 12-item Allodynia Symptom Checklist; HADS: Hospital Anxiety and Depression Scale; MIDAS, migraine disability assessment; MOH: medication overuse; n = number; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NPRS, numeric pain rating scale; SD: standard deviation.

Warm detection threshold, $_{50-60}$ and offset analgesia assessment

The experimental examinations were conducted in a quiet room with the temperature maintained at 22–24 °C, performed by one of two well-trained neurophysiology technicians. The technician administering the tests was blinded to the patients' migraine classification (episodic vs. chronic) and phase; however, full blinding was not entirely feasible. Patients in the ictal phase may have exhibited visible signs of discomfort despite being instructed not to disclose their migraine status. Additionally, complete blinding of healthy controls was challenging, as some were recruited from the institute's staff. Before the investigation, participants were familiarized with the VAS scoring system and the experimental procedures by having the tests demonstrated at the forehead contralaterally to the tested side. Both WDT, $Pain_{50-60}$, constant trials, and offset trials were measured on the forehead at the predominant headache side in participants with migraine and at a randomly selected forehead side in subjects without a predominant headache side and in HVs.

The experimental tests were performed using a 30 × 30 mm air-cooled heat probe capable of delivering a constant temperature in the range of 20 to 50 °C using a ramp (0.1–2 °C/s) and hold strategy. The probe was connected to a Q-sense CPM device (Medoc, Ramat Yishai, Israel). Before starting all the experimental procedures, conditions of abnormally low (< 35 °C) or high (> 37 °C)

local skin temperature values were ruled out by using an infrared thermometer.

The WDT and the $Pain_{50-60}$ were measured following standardized procedures [36, 37]. For the assessment of the WDT, we used the 'method of levels,' in which patients are asked to respond with 'yes' or 'no' depending on whether they perceive the warm stimulus [38, 39]. The time interval between stimuli was randomly varied within a range of 4 to 6 s. The initial temperature shift was set to 3 °C. If the participant responded 'yes,' the subsequent stimulus was delivered with a step size reduced by half. On the other hand, if the response was 'no,' the step size was doubled. Each time the response direction changed, the step size was either halved or doubled accordingly. The procedure continued until the step size was minimized to 0.1 °C, at which point the threshold was established by averaging the temperatures associated with the last 'yes' and 'no' responses. A standard sequence of level-based stimuli ultimately yielded a single threshold value. Throughout all trials, the thermode's baseline adaptation temperature was kept at 32°C, with temperature adjustments occurring at a rate of 1°C per second. Conversely, the $Pain_{50-60}$ was assessed using the 'method of limits,' where stimuli at increasing temperatures, moving from the adaptation range to the pain sensation range, were applied and the subjects were instructed to press a mouse button as soon as the pain induced by the increasing heat stimuli reached a peak of 50–60 mm on a 0-100 VAS. The test for assessing $Pain_{50-60}$ was repeated three times to verify consistency of temperature determination. Average values were calculated to obtain a single score. The interstimulus interval of 8–10 s was kept, and no clues were given to the subject at stimulus onset. In all trials, thermode adaptation temperature was set to 32°C, with rates of temperature change of 1°C/s.

After $Pain_{50-60}$ determination, three offset trials and three constant trials were applied at the forehead using a well-established procedure [4, 36, 40]. Average values were calculated to obtain a single score for offset trials and for constant trials. Offset trials included a 5-s exposure to a heating stimulus set at the individualized $Pain_{50-60}$ (T1), 5-s exposure to a temperature 1 °C higher than T1 (T2), and 20-s exposure to the same temperature as T1 (T3). Constant trials included 30-s exposure to a heating stimulus set at the individualized $Pain_{50-60}$. For subjects with $Pain_{50-60}$ greater than 48 °C, stimulation intensity was set at 48 °C for both offset and constant trials (T1 and T3). Interstimulus intervals between trials were at least 30 s, and a new trial was not applied until any sensation of pain in the stimulated area had completely disappeared, with a minimum waiting time of 20 s after the pain had subsided. Both for offset and constant trials initial increase and final decrease rates were 2 °C/s and 1 °C/s, respectively. The six trials were performed according to two pseudorandomized sequences (offset– constant– offset– offset– constant– constant, and constant– offset– constant– constant– offset– offset). For all trials, participants were asked to evaluate pain intensity by using a continuous analogue-to-digital converter of VAS (CoVAS, Medoc, Israel) anchoring at 0 = 'no pain' and 100 = 'the most intense pain imaginable'. VAS values were measured at 1-s intervals via offline analysis. Participants were unaware of the details of the offset analgesia paradigm and the study aims. All participants were instructed to carefully assess even the slightest changes in pain sensation.

Throughout the experiment, the thermode was firmly fixed on the forehead by using an elastic band with velcro. Care was taken in placing the probe, such that the best contact between probe and skin surface was achieved without causing a feeling of constriction. Subjects were informed about how to respond correctly, and, during the test, they could not see the change in temperatures on the computer screen.

Statistical analysis

Based on the previous study by Szikszay et al. [4], a sample size of $N = 60$ (30 participants with interictal episodic migraine and 30 HVs) was calculated. The calculation was based on a power of 0.85 and a type I error probability (α) of 0.05, using delta constant-offset mean values ± SD of 5.7 ± 19.3 recorded in participants with episodic migraine, and 19.4 ± 16 recorded in control subjects. The same number of 30 subjects was established for individuals with chronic migraine. Additional participants with episodic or chronic migraine were enrolled to account for potential dropouts. For episodic migraine, this also accommodated the possibility that some subjects might be in the preictal rather than the interictal phase. Regarding secondary outcome measures, although a specific number of participants with episodic migraine in the preictal, ictal, and postictal phases, as well as participants with chronic migraine with or without MOH, was not calculated a priori, we aimed for a minimum of 10 subjects in each of these subgroups. This decision was based on a previous study where significant neurophysiological differences were observed with similarly small subgroups of subjects with episodic migraine in different phases of the migraine cycle and chronic migraine without MOH [1].

Parametric statistics were employed since data were normally distributed according to the Kolmogorov–Smirnov test. ANOVAs were conducted to examine differences in the WDT and mean $Pain_{50-60}$ values. Three-way repeated-measures ANOVAs were used to analyze variations in VAS scores across time (30 levels: VAS score at every second during the 30-second offset and constant trials) and conditions (two trials: offset and

constant). Three separate ANOVAs were performed: 1) using 'group' as the between-subjects factor with three levels to compare interictal episodic migraine, chronic migraine with and without MOH, and HVs; 2) using 'phase of the migraine cycle' as the between-subjects factor with four levels to compare episodic migraine patients in the interictal, preictal, ictal, and postictal phases; and 3) using 'group' as a between-subjects factor to compare the two groups of chronic migraineurs, with or without MOH. Even though only two groups were analyzed in the latter comparison, ANOVA was used as it accounted for additional factors ('condition' and 'time'), allowing assessment of interaction effects.

To disentangle adaptation or sensitization phenomena and offset effects, the magnitude of offset analgesia was quantified by subtracting pain ratings assessed during the offset trial from those during the constant trial. Specifically, average VAS values between the 19th and 28th second, the time window in which a significant offset analgesia phenomenon was observed in HVs in the present study, were computed for both offset and constant trials. This approach was chosen as it minimizes the influence of adaptation and sensitization, allowing for a more precise focus on the offset analgesia phenomenon. The difference between the mean values during constant and offset trials (Δconstant-offset) was then calculated for each subject. A more positive Δconstant-offset value indicates a greater magnitude of offset analgesia. Conversely, negative values indicate the lack of offset analgesia phenomenon or even a paradoxical facilitation.

Three separate analyses were performed for Δconstant-offset values, considering the same groups as previously mentioned. Additionally, comparative analyses including all groups together are provided in the Supplementary Materials.

ANOVAs or t-tests were used for other continuous variables, while chi-squared test corrected for continuity was carried out for categorical variables. The Huynh–Feldt correction was applied when sphericity assumptions were violated in all ANOVAs. Duncan's post hoc test for multiple comparisons was conducted following the ANOVAs.

Two-tailed Pearson's correlation coefficients were calculated to study the relationships between Δconstant-offset value and clinical variables.

Additional statistical analyses were conducted to further explore potential factors influencing the observed results, including assessments of order effects, group differences, correlations with pain intensity, and the impact of covariates such as sex, age, and average VAS scores during constant trials. These supplementary analyses, along with detailed results, are available in the Supplementary Materials (available as supplemental digital content).

For all analyses, $P < 0.05$ was considered as significant. The statistical analyses were performed using Statsoft's Statistica version 14.2.0.

Results

We enrolled a total of 132 participants, including 68 subjects with episodic migraine (31 assessed interictally, 11 preictally, 12 ictally and 14 postictally), 34 subjects with chronic migraine (23 with and 11 without MOH) and 30 HVs. Demographic and clinical data of the subjects are summarized in Table 1.

All the recruited subjects completed all the planned experimental evaluations. The Quantitative Sensory Testing (QST) assessment was well tolerated and no drop-out occurred. No significant differences for age and gender proportions were found between HVs (mean age 37.8 years ± 17.8 SD; 19 females), participants with episodic migraine (mean age 43.6 years ± 11.9 SD; 51 females) and participants with chronic migraine (mean age 45.3 years ± 13.4 SD; 31 females).

Comparison between interictal episodic migraine, non-ictal chronic migraine and healthy subjects

No significant differences in WDT and $Pain_{50-60}$ were observed between subjects with interictal episodic migraine, chronic migraine, and HVs (Fig. 2A, B).

An interaction between the three factors (i.e., 'condition', 'time', and 'group') was observed ($F_{7,310}$ = 3.9, $P = 0.0005$) when evaluating VAS scores during offset and constant trials within the three experimental groups. Post-hoc tests were carried out to investigate differences in the VAS scores between the average values of the three constant trials and the three offset trials (Fig. 3). In HVs, a difference was observed from the 19th to the 28th s, for lower VAS values recorded during the offset trials compatible with the offset analgesia phenomenon ($P < 0.05$ at each 1-s time point). Instead, no significant differences were observed in the same time window in episodic migraine subjects, indicating lack of the offset analgesia phenomenon. Finally, a difference was observed from the 19th to the 25th s in the chronic migraine subjects, for higher VAS values during the offset trials compatible with a paradoxical facilitation of pain ($P < 0.05$ at each 1-s time point).

During constant trials, a reduction in the VAS score compared to the peak VAS recorded during the trial (indicating adaptation to the stimulus) was observed during the last 7 s in HVs, the last 8 s in episodic migraine subjects, and the last 6 s in chronic migraine subjects ($P < 0.05$ at each 1-second time point within every subgroup). No significant differences were observed among the three groups as regards VAS scores at each 1-s time point during constant or offset trials.

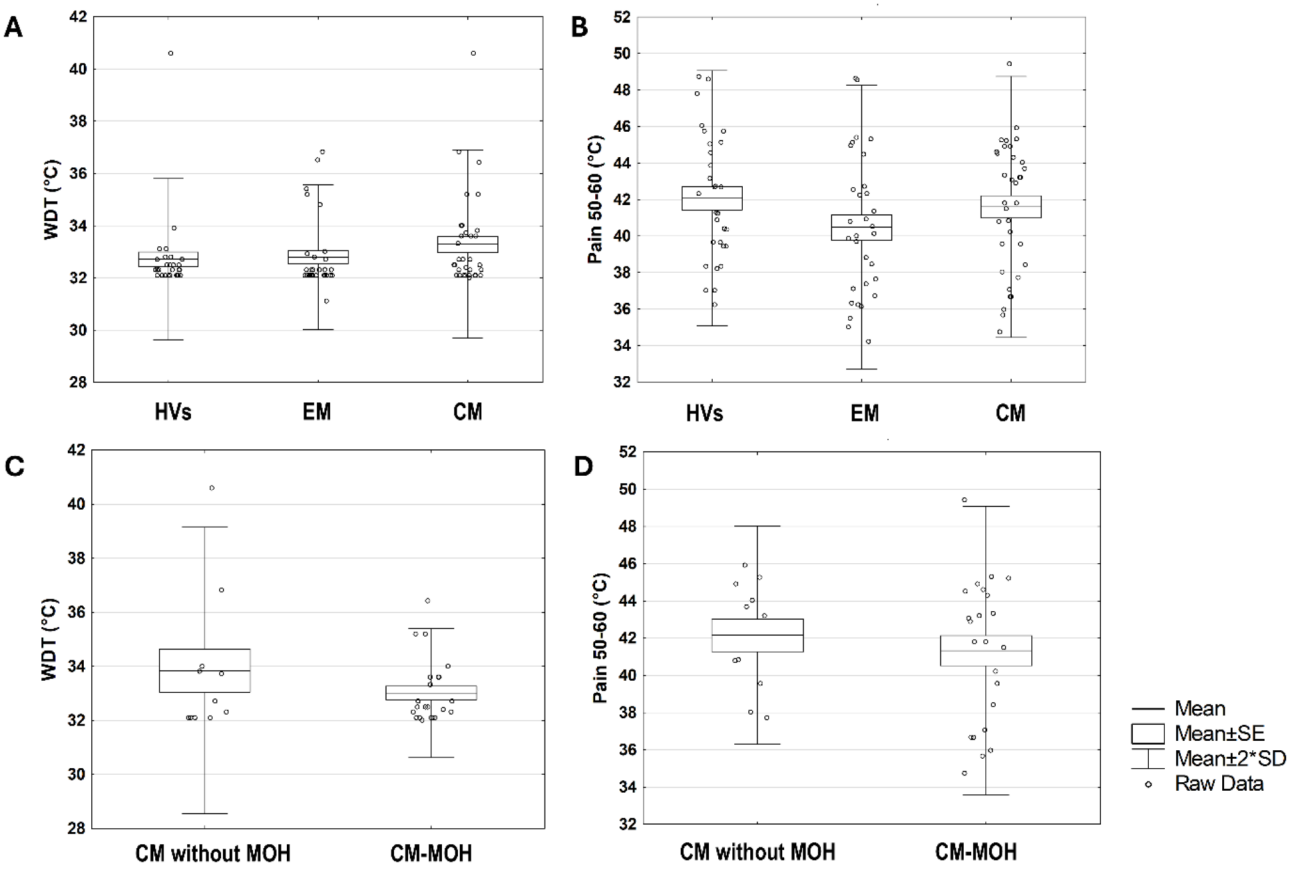

Fig. 2 Warm detection threshold and $Pain_{50-60}$ values. In **A** and **B**: subjects with episodic migraine and chronic migraine (with or without medication overuse) in comparison to healthy subjects. In **C** and **D**: comparison between subjects with chronic migraine with or without medication overuse. Mean values are reported, with standard error (box) and two standard deviations (whiskers). Dots indicate individual data points. CM: chronic migraine; EM: episodic migraine; HVs: healthy volunteers; $Pain_{50-60}$: heat pain threshold corresponding to a Visual Analog Scale peak of 50–60 mm out of 100; MOH: medication overuse headache; WDT: Warm Detection Threshold

The upper part of the figure represents the paradigm timeline for both the offset trial (blue line, showing temperature variation during the trial) and the constant trial (red line). VAS: visual analogue scale.

A mean positive Δconstant-offset value was only observed in the HVs, while negative values were recorded both in the participants with episodic and chronic migraine compared to HVs ($P = 0.001$ and 0.0005, respectively) (Fig. 4).

CM: chronic migraine; EM: episodic migraine; HVs: healthy volunteers; MOH: medication overuse headache; VAS: visual analogue scale.

Comparison of subjects with episodic migraine evaluated in different phases of the migraine cycle

No significant differences in WDT and average $Pain_{50-60}$ were observed between episodic migraine subjects assessed in the four different phases of the migraine cycle (Fig. 5).

The ANOVA performed to compare variations in VAS scores between the four subject groups revealed an interaction among the three factors 'condition', 'time', and 'phase of the migraine cycle' ($F_{13,269} = 2$, $P = 0.02$) (Fig. 6). Post-hoc tests for differences in the VAS scores between constant and offset trials were carried out considering the 19th to 28th s time window, as previously described. Higher VAS values during the offset trials, compatible with paradoxical facilitation of pain, were observed from the 19th to 24th s in subjects assessed in a preictal phase ($P < 0.05$ at each 1-s time point), and from the 19th to 26th s in subjects assessed during the ictal phase ($P < 0.05$ at each 1-s time point). Lower VAS values during the offset trials, compatible with offset analgesia phenomenon, were observed only in the subjects assessed in the postictal phase from the 23rd to 29th s ($P < 0.05$ at each 1-s time point). A reduction in the VAS score compared to the peak VAS during the constant trials, indicating adaptation to the stimulus, was observed during all preictal (peak vs. last 15 s), ictal (peak vs. last 5 s) and postictal (peak vs. last 6 s) phases ($P < 0.05$ at each 1-s time point).

The upper part of the figure represents the paradigm timeline for both the offset trial (blue line, showing

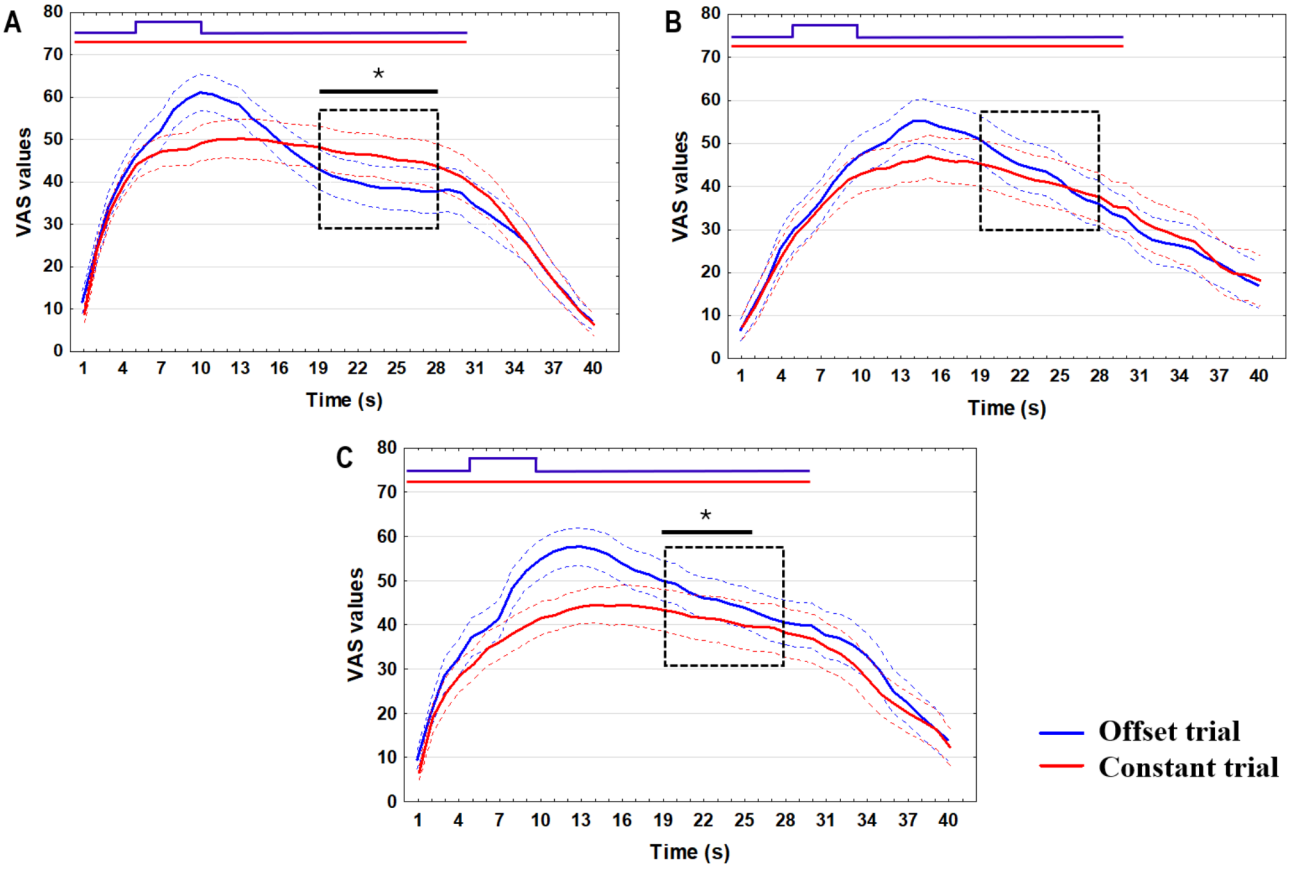

Fig. 3 VAS values recorded during the constant trial and the offset analgesia trial. Findings are reported for healthy volunteers (**A**), subjects with episodic migraine during the interictal phase (**B**), and subjects with chronic migraine with or without medication overuse (**C**). Mean values are reported. Dashed lines represent standard error of the mean. The horizontal bar with an asterisk indicates significant differences ($P < 0.05$ at each 1-s time point) in the time window between 19 s and 28 s (indicated by the box with a dashed line). Note the absence of the offset analgesia phenomenon in episodic migraine subjects during the interictal phase and the paradoxical facilitation of pain in chronic migraine subjects

temperature variation during the trial) and the constant trial (red line). VAS: visual analogue scale.

A mean positive Δconstant-offset value was only recorded in the postictal subgroup, while negative values were recorded during both the preictal and ictal phases (Fig. 4). A difference between subgroups was observed ($p = 0.001$). At post-hoc analysis, lower values were recorded in ictal vs. interictal subgroup, while significant higher values were recorded in the postictal subgroup vs. all other subgroups, also including episodic migraine subjects in the interictal phase ($P < 0.05$).

Comparison of chronic migraine with and without MOH

No significant between-group differences were observed in the WDT and $Pain_{50-60}$ values (Fig. 2C, D). An interaction ($F_{3,108} = 3.5$, $P = 0.01$) between the three factors (i.e., 'condition', 'time', and 'group') was observed (Fig. 7). The post-hoc analysis for differences in the VAS scores in the 19th to 28th s time window showed higher VAS values in the chronic migraine without MOH subgroup during the offset compared to the constant trials, compatible with paradoxical facilitation of pain ($P < 0.05$ at each 1-s time point). No significant differences in the VAS values between offset and constant trials were observed in the chronic migraine with MOH subgroup. A reduction in the VAS score compared to the peak VAS during the constant trials was observed during the last 3 s and 7 s in chronic migraine with or without MOH, respectively ($P < 0.05$ at each 1-s time point). T-test showed a significantly lower mean Δconstant-offset value in chronic migraine with vs. without MOH ($P = 0.005$) (Fig. 4).

The upper part of the figure represents the paradigm timeline for both the offset trial (blue line, showing temperature variation during the trial) and the constant trial (red line). VAS: visual analogue scale.

Correlation between the degree of offset analgesia impairment and clinical variables

Two-tailed Pearson's correlation coefficients showed a negative correlation of Δconstant-offset values with both ASC-12 (r = -0.25, $P = 0.040$) and NPRS (r = -0.296, $P = 0.020$) scores when considering the total number of

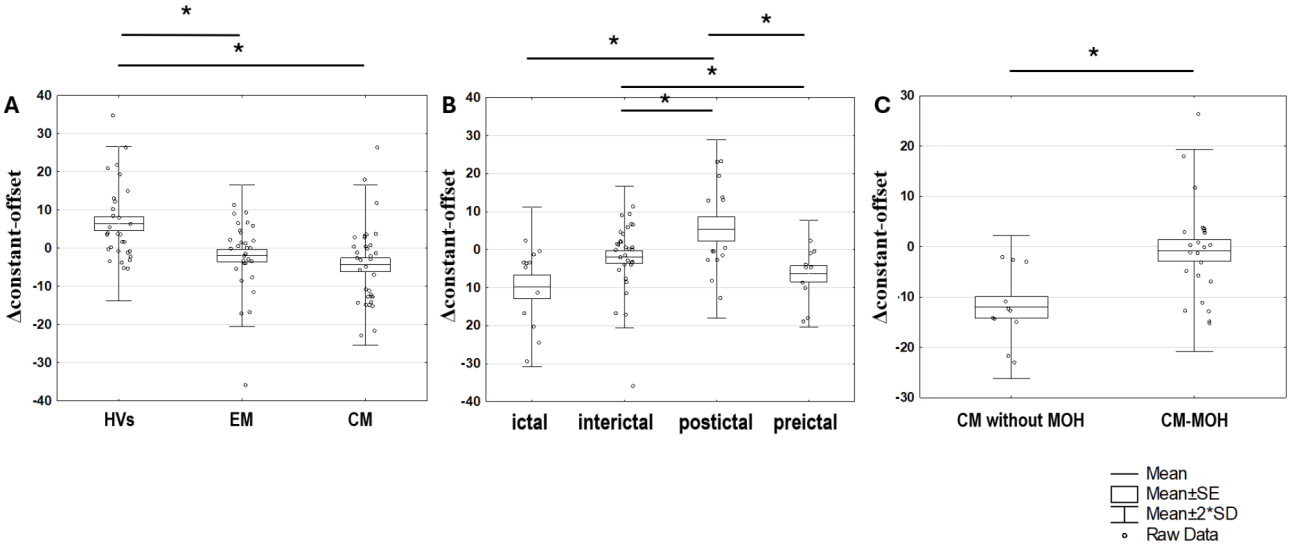

Fig. 4 Magnitude of offset analgesia (positive values) or paradoxical facilitation of pain (negative values). Magnitude of offset analgesia is calculated as a difference between the mean VAS value recorded during the constant trial and the mean VAS value recorded during the offset trial (Δconstant-offset) in the time window between 19 s and 28 s. In A: differences between healthy volunteers, subjects with interictal episodic migraine and subjects with chronic migraine with or without medication overuse. In B: differences between different subgroups of patients with episodic migraine assessed during different phases of the migraine cycle. In C: differences between subjects with chronic migraine with or without medication overuse headache. The time window from the 19th to the 28th second (indicated by the box with a dashed line) was considered for the analyses (see text for details). Mean values are reported, with SE (box) and 2SD (whiskers). Dots indicate individual data points. The horizontal bars with an asterisk indicate significant differences ($P < 0.05$). Note: post-hoc comparisons following ANOVA were performed when more than two groups were compared

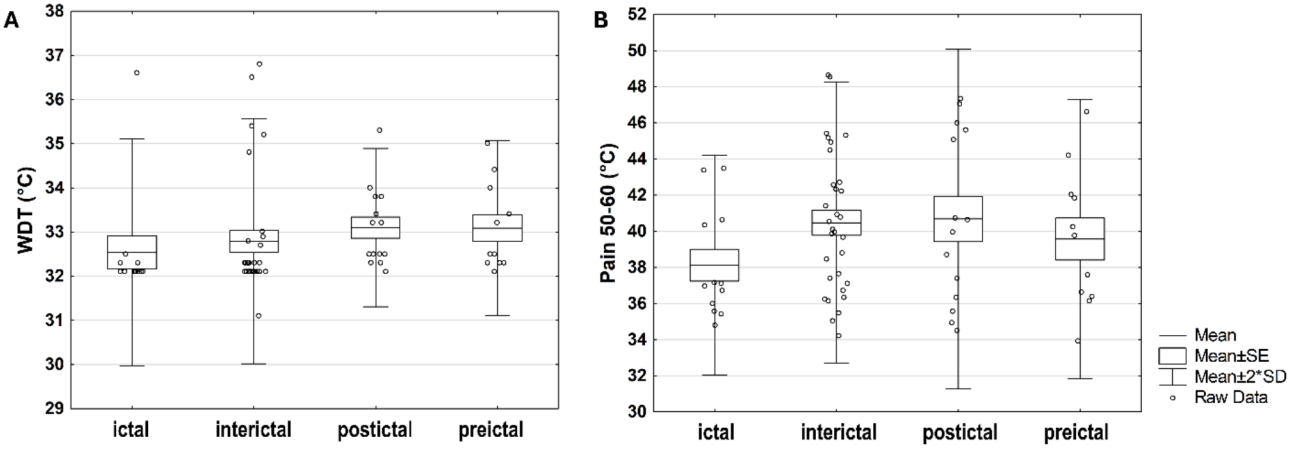

Fig. 5 Warm detection threshold (**A**) and $Pain_{50-60}$ (**B**) during different phases of the migraine cycle. Mean values are reported. Mean values are reported, with standard error (box) and two standard deviations (whiskers). Dots indicate individual data points. $Pain_{50-60}$: heat pain threshold corresponding to a Visual Analog Scale peak of 50–60 mm out of 100; WDT: Warm Detection Threshold

subjects with interictal episodic migraine and the subjects with chronic migraine (participants with episodic migraine assessed during the preictal, ictal, and postictal phases were excluded to mitigate the influence of migraine attack-related changes on the offset analgesia phenomenon). No other correlations were observed with other clinical variables, including frequency of attacks, disease duration, as well as HADS and MIDAS scores.

Discussion

The present findings support our primary hypothesis of greater offset analgesia dysfunction in chronic compared to episodic migraine patients, specifically in the subgroup of chronic patients without MOH, where paradoxical responses were observed. Cyclical offset analgesia changes were observed throughout the migraine cycle in episodic migraine patients.

Migraine pain is transmitted by peripheral trigeminal neurons to central neurons in the spinal trigeminal nucleus (SpV) [41]. Ascending nociceptive signals are

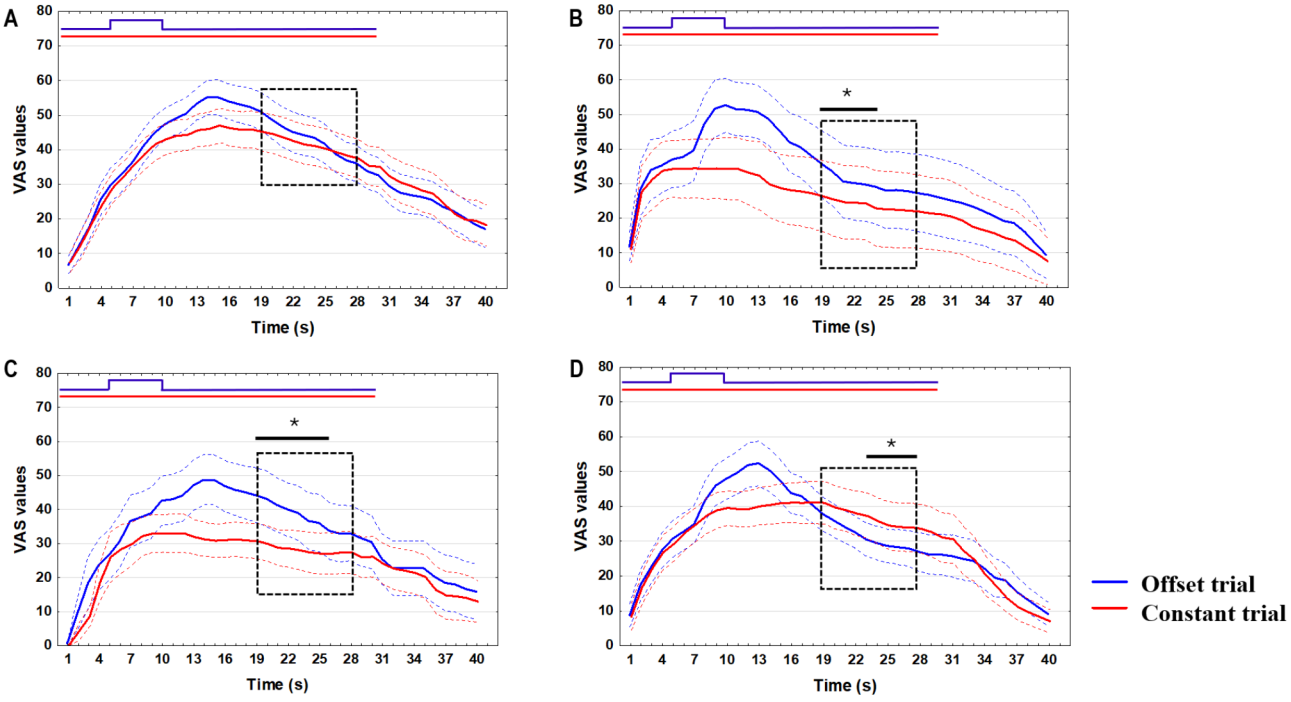

Fig. 6 VAS values recorded during the constant and offset analgesia trials throughout the migraine cycle. Findings are reported for the interictal (**A**), preictal (**B**), ictal (**C**), and postictal (**D**) phases. Mean values are reported. Dashed lines represent standard error of the mean. The horizontal bar with an asterisk indicates significant differences ($P < 0.05$ at each 1-s time point) in the time window between 19 s and 28 s (indicated by the box with a dashed line). Note that subjects with episodic migraine during the interictal phase are depicted in Fig. 3B. Observe the presence of the offset analgesia phenomenon only in the subgroup of subjects in the postictal phase, while a paradoxical facilitation of pain is observed in the other two subgroups

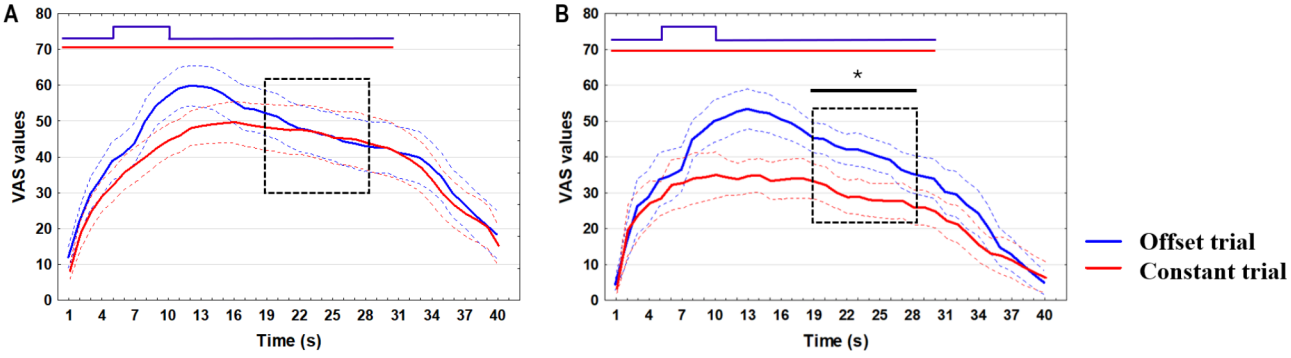

Fig. 7 VAS values recorded during the constant and offset analgesia trials in subjects with chronic migraine. Findings are reported for patients with (**A**) or without (**B**) medication overuse. Mean values are reported. Dashed lines represent standard error of the mean. The horizontal bar with an asterisk indicates significant differences ($P < 0.05$ at each 1-s time point) in the time window between 19 s and 28 s (indicated by the box with a dashed line), compatible with paradoxical facilitation of pain

modulated by descending inputs from brainstem areas, particularly the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) [42, 43]. PAG suppresses SpV activity [44, 45], while RVM neurons can either enhance (ON cells) or inhibit (OFF cells) pain signals (Fig. 8) [42, 46–49].

In this study, we recorded lower $Pain_{50-60}$ thresholds in both healthy subjects and patients compared to previous reports, which may be influenced by a combination of methodological and pathophysiological factors. From a methodological standpoint, differences in assessment methods (e.g., $Pain_{50-60}$ vs. $Pain_{60}$), instrumentation (air-cooled vs. water-cooled thermode), and the tested region (trigeminal vs. extracephalic sites) could contribute to these discrepancies. However, beyond these technical aspects, our findings may also reflect phase-dependent fluctuations in pain sensitivity throughout the migraine cycle. Peng and May [50] highlight that heat pain thresholds progressively decrease toward the ictal phase, suggesting that endogenous pain modulation dynamically

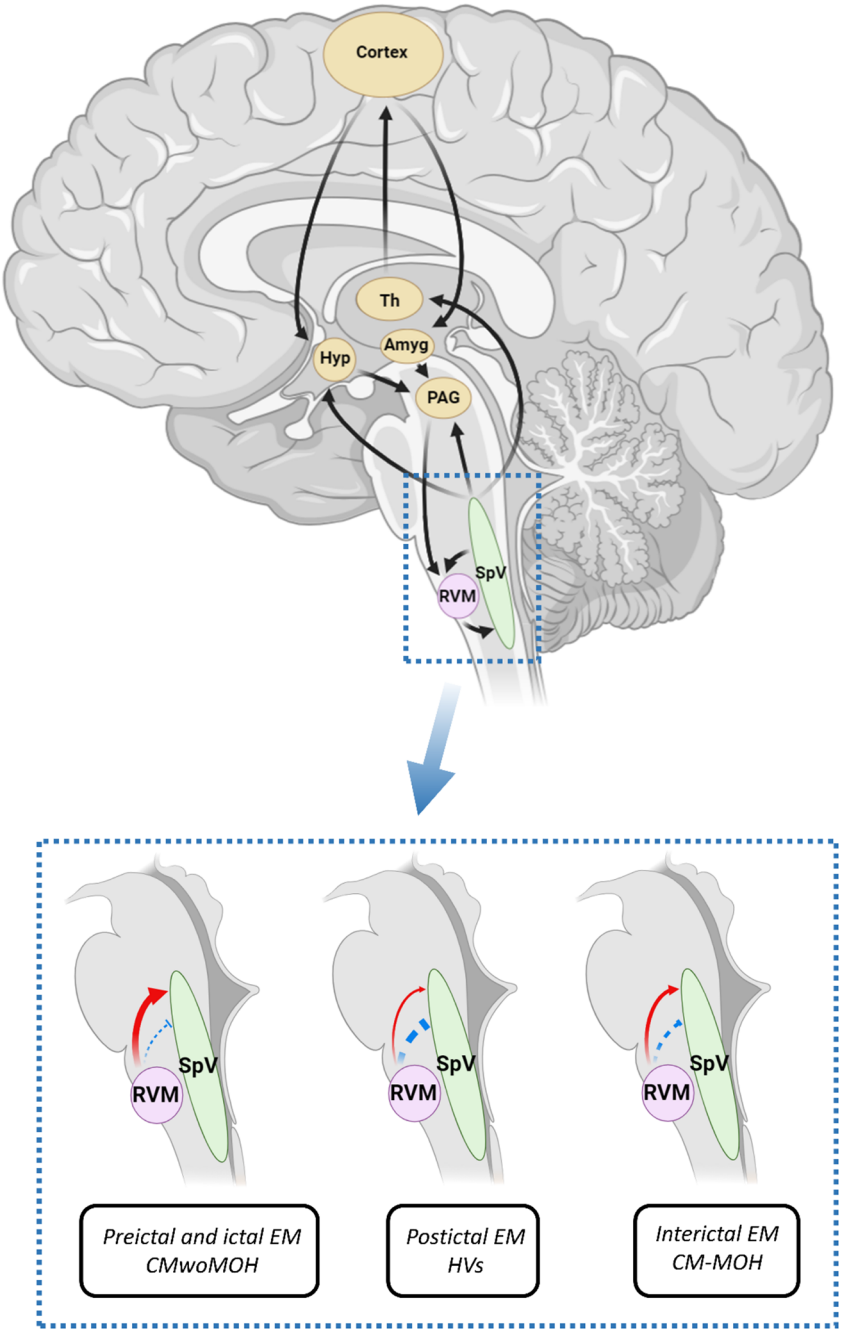

Fig. 8 Schematic representation of the pain modulatory circuitry and ascending nociceptive pathway. The figure illustrates a theoretical model of the pathophysiological mechanisms underlying migraine. In the lower dashed box, the connections between the RVM and the SpV are magnified, distinguished into pronociceptive (red arrow) and antinociceptive (blue dashed line) with respect to the ascent of nociceptive sensory information. In the centre, a physiological balance favouring the antinociceptive connections is depicted, which is hypothesised to contribute to the phenomenon of offset analgesia observed in HVs and episodic migraineurs during the postictal phase. On the left, an imbalance favouring the pronociceptive projections is illustrated, hypothesised as a possible explanation for the paradoxical facilitation of pain observed in chronic migraineurs without MOH and episodic migraineurs during the preictal and ictal phases. Finally, on the right, a functional imbalance still favouring the pronociceptive projections, albeit less pronounced than the previous one, is represented, which may underlie the absence of the offset analgesia phenomenon in episodic migraineurs during the interictal phase and in chronic migraineurs with MOH. Amyg: amygdala; Hyp: hypothalamus; HVs: healthy volunteers; MOH: medication overuse headache; PAG: periaqueductal gray matter; RVM: rostroventromedial medulla; SpV: spinal trigeminal nucleus; Th: thalamus (figure made by Biorender.com)

oscillates across different migraine stages. While we did not observe significant differences in $Pain_{50-60}$ values across phases, the overall lower thresholds in migraine patients may still indicate subclinical sensitization phenomena that fluctuate throughout the cycle. Similarly, the increased variability in WDT observed in migraine patients, particularly the presence of values exceeding the expected normative range, may also reflect phase-dependent fluctuations in sensory processing [50].

Functional changes in pain modulation networks are thought to contribute to migraine onset, maintenance, and associated symptoms [29, 42]. Most studies on endogenous pain control have focused on episodic migraine subjects in the interictal phase, limiting understanding of pain-modulation mechanisms across the migraine cycle. Consistent with Szikszay et al. [4], we confirm that the offset analgesia phenomenon was absent or reduced in the trigeminal area in most, but not all, episodic migraine subjects during the interictal phase. No significant differences in $Pain_{50-60}$ values and responses to tonic pain stimuli were observed between interictal episodic migraineurs and HVs, suggesting a specific disruption in modulatory mechanisms for dynamic painful stimuli. Notably, our findings reveal a shift toward paradoxical pronociceptive facilitation in the preictal and ictal phases, potentially implicating the RVM in migraine onset. This could support the theoretical hypothesis of an imbalance favoring increased activation of ON pro-nociceptive neurons over OFF anti-nociceptive neurons during the preictal phase (Fig. 8).

Marciszewski et al. [51] observed cyclical changes in brainstem function during the migraine cycle using fMRI. Specifically, in episodic migraine subjects assessed preictally, they found that increased SpV activation in response to repeated tonic noxious stimuli correlated with reduced self-reported pain and diminished RVM-SpV connectivity, suggesting a homeostatic shift favoring OFF cell input to the SpV. In our study, lower VAS values during the constant trials in both preictal and ictal migraineurs compared to the interictal phase were observed, although these differences were not statistically significant. This suggests that the paradoxical pronociceptive facilitation observed during the preictal and ictal phases may reflect a cyclical dysfunction specifically involving temporal filtering mechanisms for dynamic noxious stimuli (Fig. 8). In particular, it is possible that during these phases of the migraine cycle, the 1 °C temperature increase during T2 in the offset trial induced paradoxical pronociceptive mechanisms that are not activated during constant trials. Therefore, the results should be interpreted by considering the possible interplay between different anti-nociceptive and pronociceptive mechanisms, which may be differentially engaged by tonic versus dynamic noxious stimuli. The restoration of the offset analgesia phenomenon during the postictal phase suggests that endogenous anti-nociceptive mechanisms may continue to be activated in episodic migraine, potentially aiding in terminating migraine pain.

Functional changes in brainstem pain modulatory areas before migraine onset may be influenced by higher brain regions. Mungoven et al. [8] reported reduced connectivity between the dorsolateral prefrontal cortex (dlPFC) and key cortical, subcortical, and brainstem areas (e.g., RVM and dorsolateral pons) involved in pain modulation in episodic migraine subjects preictally. A functional near-infrared spectroscopy study in HVs found that right dlPFC activation during offset heat stimuli was associated with deactivation of medial prefrontal and somatosensory cortices, suggesting the right dlPFC's role in inhibiting ascending noxious inputs via subcortical pathways [27].

A paradoxical pronociceptive response during the T3 period of the offset trials, similar to that observed in most episodic migraine during the preictal and ictal phases, was observed in chronic migraine without MOH. This may reflect a persistent shift from anti-nociceptive to pro-nociceptive mechanisms, preventing the PAG-RVM system from resetting after migraine onset, leading to a 'never-ending attack' (Fig. 8). This perspective is supported by animal studies showing that descending facilitatory input from the RVM can trigger and sustain hyperalgesia in chronic pain [52], and by clinical research linking dysfunctions in descending pain inhibitory systems to chronic pain conditions [53]. Migraine is considered a threshold disease, where recurring attacks progressively lower the threshold for future episodes, contributing to chronification [54, 55]. This may involve a decline in inhibitory pain modulatory responses to external stressors. Solstrand Dahlberg et al. [56] found increased PAG connectivity with the primary somatosensory cortex (face representation) and pain expectancy areas (e.g., supplementary motor area) in interictal migraineurs with higher attack frequency compared to HVs, alongside reduced connectivity between the PAG and the prefrontal cortex, a key region in the descending pain modulatory system. Disease duration and attack frequency have also been found to correlate with reduced PAG-putamen connectivity and basal ganglia morphological changes in migraineurs [56–58]. Given the basal ganglia's role in modulating acute and chronic pain and analgesic responses [59], their diminished engagement may reflect another manifestation of impaired pain modulatory system in migraine.

Our findings suggest that the pathophysiological mechanisms of chronic migraine may differ between patients with and without MOH. In chronic migraine with MOH, the absent or reduced offset analgesia phenomenon in most, but not all, subjects (similar to interictal episodic

migraine) suggest additional mechanisms beyond dysfunction of endogenous pain control, such as central sensitization, cortical hyperexcitability, and neurogenic inflammation [60]. Subjects with chronic migraine with MOH show increased sensitization of somatosensory cortical evoked responses and potentiation to repetitive non-painful stimuli [61]. In contrast, subjects with chronic migraine without MOH exhibit initial sensitization but no response potentiation with repeated stimulation [62, 63]. Recent neurophysiological evidence showed that central neuronal circuits are highly sensitized at both thalamocortical and cortical levels in subjects with chronic migraine with MOH, likely as a direct consequence of persistent administration of analgesics [64]. Indeed, according to studies on rodents, persistent administration of various classes of analgesics causes central sensitization [65, 66], leading to increased activation of the SpV [67] and enhancing susceptibility to evoked cortical spreading depression [67–70]. In addition, the mechanisms underlying offset analgesia may provide further insights. Offset analgesia primarily depends on A-delta fibers, while C-fibers are more closely associated with central sensitization [19, 71]. This distinction could explain why no differences in offset analgesia responses were found between subjects with migraine assessed interictally (in which central sensitization may be not as strong as in chronic migraine patients) and subjects with chronic migraine associated to MOH, despite their distinct phenotypes. This might, in fact, be due to the presence of distinct pathophysiological mechanisms in the latter group of subjects, such as central sensitization, which are not adequately assessed by the offset analgesia paradigm.

The correlation between Δconstant-offset values and ASC12 and NPRS scores suggests that an imbalance between descending antinociceptive and pronociceptive mechanisms may enhance central sensitization, amplifying pain signaling [72, 73]. Central sensitization, a key factor in cutaneous allodynia, is more common in chronic migraine with MOH than in episodic migraine and is a predictor of migraine chronification [71, 74, 75]. Dysfunction in the RVM, leading to prevailing descending facilitation, is considered crucial for allodynia development [65, 76]. Supporting this, RVM inactivation with bupivacaine blocked cephalic and extracephalic allodynia induced by inflammatory mediators in rat models [76].

The present study has several limitations. First, we acknowledge the relatively small sample sizes of the preictal, ictal, postictal, and chronic migraine without MOH cohorts, as well as the absence of longitudinal assessments. The cross-sectional design limits our ability to track individual changes across different migraine phases, preventing definitive conclusions regarding the modulation of offset analgesia responses over time. While our findings suggest potential variations in endogenous pain control mechanisms across the migraine cycle, these remain speculative and require confirmation through longitudinal studies with larger cohorts to establish a clearer causal relationship. Furthermore, while our data indicate predominant group differences, individual variability should be considered when interpreting the findings. In the interpretation of the findings regarding subjects with chronic migraine, caution is required because they were assessed only during a phase of non-exacerbated pain, which may not be easily distinguishable from preictal or postictal phases. In the absence of a consensus identification and definition of the different phases of pain during chronic migraine, the selection of a pain intensity > 6 at the NRS scale to identify an ongoing pain exacerbation seemed the best trade-off based on clinical evidence. A potential confounder could be the unbalanced gender proportion of the participants, which is however reflecting the higher prevalence of migraine in females. Of note, our control sample was matched for gender to mitigate the confounding effects of this discrepancy. Additionally, we cannot exclude the possibility that prophylactic medications could have affected the offset analgesia phenomenon in chronic migraine subjects. Nevertheless, it is unlikely that these medications significantly affected our findings, as fewer than half of the patients were on stable prophylactic therapy with a single drug from various classes, and they still satisfied the diagnostic criteria for chronic migraine, suggesting that the therapy was not effective. Moreover, current evidence does not support the notion that centrally acting drugs, including serotonin-noradrenaline reuptake inhibitors, antiepileptic drugs and beta blockers, could modulate offset analgesia [77, 78]. Furthermore, our experimental paradigm did not include the assessment of offset analgesia outside the trigeminal area, which could have provided additional insights. It is worth noting, however, that in a previous study assessing offset analgesia in subjects with migraine [4], the authors failed to detect significant differences between subjects with migraine evaluated interictally and healthy controls when offset analgesia was assessed in an extratrigeminal area (forearm). Finally, the experimental paradigm of offset analgesia may capture only dysfunctional aspects related to endogenous pain control underlying the processing of dynamic painful stimuli. A combined approach using different paradigms, including more sensitive tests for identifying central sensitization phenomena, should be applied in future studies to gain a more comprehensive understanding.

In conclusion, our results provide an opportunity to connect preclinical and clinical findings regarding the functioning of descending pain modulation systems in different migraine phenotypes. Future longitudinal

studies will have to examine how changes in the offset analgesia phenomenon relate to clinical progression and response to prophylactic treatments, to clarify its potential as a biomarker. Understanding the mechanisms underlying alterations in the offset analgesia phenomenon in migraine may ultimately pave the way for the development of new pharmacological or non-pharmacological therapeutic approaches.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-01995-4.

Supplementary Material 1

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Author contributions
GC conceived the study and drafted the protocol, which were subsequently refined in meetings of the investigators. EA, C., EG, and NG were responsible for the performance of the study under the supervision of CT, MT, RD, and MC. EA and CC contributed to data management. GC carried out the statistical analysis. GC drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability
Raw data used in this study are available in the Zenodo repository at 10.5281/zenodo.12742349.

Declarations

Competing interests
The authors declare no competing interests.

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